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The Interleukins

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ABSTRACT. In this review we have summarized the large mass of information that has accumulated in recent years relative to the heterogeneous group of molecules known as the interleukins (IL), the lymphokines, and the cytokines that control the growth and differentiation of cells of the hematopoietic and lymphoid lineage and cells of other lineages. Our intent is to provide the informed generalist with a body of information with which to interpret and understand forthcoming studies of this important class of molecules, particularly those with clinical import. (*Pediatr Res* 24:549–557, 1988)

The nomenclature governing IL has arisen haphazardly from the order of their discovery and other "trivial" considerations. Thus, the various designations frequently have little to do with the origin or the function of the individual molecules. An additional deficiency of the current nomenclature is that the IL do not include the various interferons and certain other factors that, for all intents and purposes, are also IL. On this basis, it is not unreasonable to expect that a new nomenclature will eventually be devised. In the present work, we have used the current nomenclature and have provided a more or less complete list of synonyms. As an additional frequently used convention, we sometimes refer to the IL as lymphokines when they are produced by lymphocytes and as cytokines when they are produced by nonlymphoid cells.

IL-1

IL-1 was first identified as a lymphokine by Gery and Waksman (1) who showed that macrophages produce a factor capable of augmenting T cell responses to antigens and mitogens. This factor ultimately proved to have an extraordinary variety of functions and was in fact shown to be identical with several cytokines identified both before and after its discovery. Among the latter are endogenous pyrogen (a factor known to cause fever), leukocytic endogenous mediator (an inducer of acute phase reactants and neutrophilia) catabolin, osteoclast-activating factor and hemopoietin-1 (2–4). IL-1 is a phylogenetically old molecule that predates the evolution of lymphocytes and immunoglobulins; on this basis it is not surprising that its activities "transcend" immune function.

IL-1 consists of not one but two very distinct molecules (IL-1α and IL-1β) (Table 1) that are products of separate genes (both of which, in humans, are on chromosome 2) (5–8). The two IL-1 are structurally quite dissimilar except for a region of homology which is likely to be the recognition site for the IL-1 receptor (9). This surprising difference may reflect the fact that the two forms

of IL-1 occupy separate biologic niches, IL-1β being the predominant secreted form and IL-1α being the main membrane-bound form (10). In recent years, considerable evidence has accrued showing that the membrane-bound form of IL-1 is a biologically active molecule that can participate in the costimulation of T cells by antigen-pulsed macrophages.

IL-1 is produced by macrophages and a wide variety of other cells such as keratinocytes, astrocytes, and mesangial cells (11). In macrophages IL-1 production is stimulated by a variety of agents such as lipopolysaccharide (LPS), phorbol esters, leukotrienes, immune complexes, UV irradiation, and agents that induce phagocytosis (11, 12). In addition, T cells interacting with macrophages, either by cell-cell contact or via lymphokines, can induce IL-1 synthesis (11, 12). Agents that suppress IL-1 secretion include those which down-regulate immune responses generally such as cyclosporin A, corticosteroids, and prostaglandins (13–15); in addition, because IL-1 is itself a stimulator of corticosteroid and prostaglandin synthesis, IL-1 may have negative feedback effects on IL-1 production. Finally, naturally occurring but as yet incompletely characterized IL-1 inhibitors have been identified in febrile patients and pregnant women; the existence of such inhibitors indicate that negative feedback of IL-1 synthesis may normally occur *in vivo* (16).

IL-1 activity is mediated by widely distributed IL-1 receptors. Recent work suggests that the latter occur as high affinity and low affinity receptors and that both IL-α and IL-β bind to the same receptor (17, 18). IL-1 binding to its receptor on T cells is an activation signal accompanied by an increase in protein kinase C activity and increase in cytosolic calcium concentration (12). However, this is not the case with neutrophils, a fact that may explain the lack of IL-1 effects on neutrophil chemotaxis and oxidative metabolism. Finally, the binding of IL-1 to its receptor leads to internalization of the receptor-ligand complex and down-regulation of receptor expression; such internalized IL-1 is not degraded and may be transported into the nucleus where it can conceivably exert control on intranuclear processes (18, 19).

The diverse activities of IL-1 reflect both direct effects of this interleukin as well as indirect effects brought about by mediators released secondary to IL-1 secretion. One way of organizing and analyzing these activities is based on the unifying view that IL-1 is the IL most responsible for the inflammatory changes regularly induced by pathogenic organisms or autoimmune processes (1, 12). Thus, in the CNS, IL-1 acts on the hypothalamic thermoregulatory center and other CNS centers to cause fever and sleep and acts in many areas of the CNS to increase secretion of various neuropeptides (including endorphins), corticotropin-releasing factor, and ACTH; the latter, in combination with direct effects of IL-1 on the adrenal gland, leads to increased circulating steroid levels and thus the many inflammatory changes brought about by steroids. Similarly, IL-1 acts as an inflammatory mediator in the liver, where it increases synthesis of acute phase reactants and metallothionines and decreases synthesis of albumin. In addition, in this organ it inhibits lipoprotein lipase synthesis and thus causes decreased lipid utilization and lactic acidosis.

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Table 1. *IL*

Factor	Form	Synonyms	Major sources	Major effects
IL-1	β	Endogenous pyrogen	Macrophages; also: endothelial epithelial, fibroblast, and other cell types	Proliferation and differentiation of T and B cells and other cell types. Fever, tissue catabolism, chemotaxis
	α		Membrane bound form of IL-1 on macrophages	Lymphocyte activation and differentiation
IL-2		T cell derived growth factor T cell replacing factor Killer helper factor	Activated T cells	Cofactor for growth and differentiation of T cells and B cells. Increased cytotoxic activity of T and NK cells and monocytes.
IL-3		Multi-CSF (human) Mast cell growth factor (mouse) Burst promoting activity Erythroid CSF Eosinophil CSF	Activated T cells	Stimulates growth of multipotential stem cells and erythroid and myeloid progenitors. In mouse supports mast cell growth.
IL-4		BCGF BSF-1	T cells	Growth factor for: B cells and some T cells, erythroid, myeloid, and megakaryocytic precursors, increases HLA Class II expression, Increases IgG1, IgE (mouse).
IL-5		BCGF-II IgA-enhancing factor Eosinophil CSF	Activated T cells	Induces differentiation of eosinophils, augments proliferation of activated B cells (in mouse), enhances IgA production
IL-6		IFN-β BCDF BSF-2 Hepatocyte-stimulating factor	Fibroblasts, macrophages Minor: T cell lines	B cell differentiation Hepatocytes: acute phase reactants Weak anti-viral effects
TNF	α	TNF Cachectin	LPS stimulated Macrophages	Necrosis of tumors Wasting of chronic disease Pyrogenic Endotoxic shock Bone resorption
	β	Lymphotoxin	Lymphocytes	Same as α

Other less organ-specific inflammatory effects of IL-1 include its capacity to augment connective tissue cell growth and collagen formation, to increase bone resorption (osteoclast activity) and to induce prostaglandin synthesis. In addition, IL-1 augments the catabolic effects of tumor necrosis factor (TNF) and is synergistic with the latter in the generation of hypertension and the capillary leak syndrome. Finally, IL-1 has notable inflammatory effects on the vascular system where it acts to deliver inflammatory cells to sites of tissue injury and to contain invasive pathologic processes. These effects include the enhancement of endothelial cell proliferation, the release of potent vasodilators, and the initiation of clot formation.

Interfacing with these "general" activities of IL-1 are the effects of this interleukin on hematopoietic and lymphoid cells. First, IL-1 stimulates the synthesis of colony-stimulating factors and/or acts as a colony-stimulating factor itself (hemopoietin-1 activity) (20, 21). Thus, IL-1 is an important component of the bone marrow responses to inflammatory influence. Second, IL-1 plays a key role as a second messenger in antigen/mitogen-induced activation of T cells; it acts in combination with the latter stimuli to cause maximal expression of IL-2 receptors and the production of IL-2 (11, 22). This central activity of IL-1 is actually its defining feature as an IL (see Fig. 1) and establishes the molecule as one whose effects are primary to many other lymphokine effects (at least as far as the T cell is concerned) (Fig. 1). Third, IL-1 has important effects on other (non-T) lymphoid cells and on macrophages. In this context, it acts on activated B cells (usually in association with other lymphokines) to induce cell proliferation and differentiation (23, 24) and on macrophages to causes synthesis of prostaglandins and cytokines and to bring about increased macrophage cytotoxic activity (25, 26).

These various properties of IL-1 obviously help the organism to eliminate exogenous noxious agents or injurious processes of an endogenous origin. It is important to note, however, that
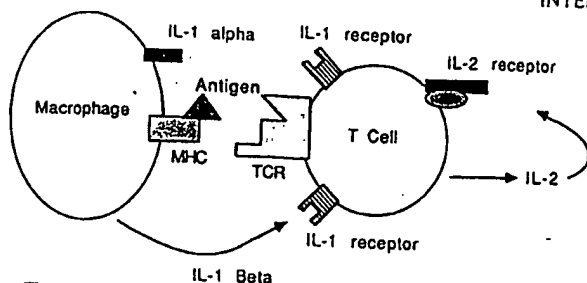
Fig. 1. IL-1 (either as membrane-bound IL-1α or soluble IL-1β) is a costimulant of the T cell during Ag-driven stimulation of the T cell via the T cell receptor (TCR). Such co-stimulation results in IL-2 production and IL-2 receptor expression and further T cell proliferation. MHC, major histocompatability complex.

under certain circumstances these very same properties allow IL-1 to become a mediator of tissue injury. This is seen most clearly in studies of the pathogenesis of arthritis, wherein it has been shown that IL-1 can induce arthritis when injected into a normal joint and can enhance arthritis produced by other stimuli when given systemically (27). These pathologic effects of IL-1 may be due to the fact that, as alluded to above, IL-1 can act as a chemotactic factor, cause the release of prostaglandins and collagenase, induce osteoclasis, and bring about degranulation of leukocytes and the release of proteolytic enzymes and other destructive substances. Based on what is known about IL-1 in arthritis one might postulate that many autoimmune diseases are facilitated, if not caused by IL-1-mediated effects. On this basis it becomes reasonable to postulate that an IL-1 antagonist, perhaps one structurally related to one of the aforementioned natural IL-1 inhibitors, would serve as a mode of therapy for immunologically mediated tissue injury.

At present there are no clearly documented diseases caused by primary IL-1 deficiency or overproduction. However, given the potent and ubiquitous effects of this very central IL either of these kinds of defects may well be lethal at a very early stage and thus escape detection by current methods.

IL-2

The existence of mitogenic substances acting on lymphocytes or T cell lines has been known for over 20 yr. but it was not until Morgan et al. (28) and Gillis and Smith (29) showed that a factor was necessary for normal T cell proliferation that the identification and characterization of the factor that became known as IL-2 began in earnest. In humans IL-2 is a 15.4-kDa glycosylated protein encoded by a gene on the long arm of chromosome 4 (30). It acts on activated T cells and (to a lesser extent) B cells, as well as with natural killer cells and thymocytes, causing these cells to proliferate and/or manifest differentiated cell function (e.g. cytotoxicity) (30, 31).

T cells display both a high affinity and a low affinity IL-2 receptor. The high affinity receptor is a heterodimer which is composed of a p55 moiety (known as the Tac antigen) which binds IL-2 with low affinity and a p75 moiety which binds IL-2 with intermediate affinity (32, 33). Activated lymphocytes express both high affinity (p75/p55) and low affinity (p55) receptors, whereas large granular lymphocytes (including NK cells) express receptors of intermediate affinity (p75) (33). IL-2 receptors are also found on B cells and various cells of the macrophage/monocyte lineage. Of interest, IL-2 receptor expression on HTLV-1-virus infected T cells is increased by 5- to 10-fold over that of mitogen-activated T cells. This may be due to the fact that the virus produces a protein (a product of the viral tat gene) which acts on an IL-2 receptor gene promoter to increase IL-2 receptor transcription (34). It is reasonable to suppose that the

tat gene product may be a homologue of a normal intracellular protein involved in IL-2 receptor expression.

IL-2 is synthesized by both T cells (CD4 cells > CD8 cells) and large granular lymphocytes (31). A variety of stimuli induce IL-2 synthesis including specific antigens, antibodies reacting with cell surface molecules important in activation pathways (CD3 and CD2 antigens), and nonspecific activating substances such as phorbol esters and mitogens. As mentioned earlier, IL-1 is necessary for maximal antigen- or mitogen-induced T cell IL-2 synthesis and may even be necessary for IL-2 synthesis to occur at all. The uncertainty relating to this issue is due to the fact that T cell stimulation requires some form of cell presentation of antigen or mitogen bound to cells which contain IL-1 in their membranes; thus, stimulation of T cells occurring in the absence of fluid-phase IL-1, may actually be due to membrane-bound IL-1. This being said, T cell activation and IL-2 production can be brought about in the absence of IL-1 by various chemical stimuli (e.g. phorbol esters and ionomycin). As for inhibition of IL-2 synthesis, this is brought about by a variety of immunosuppressive substances such as glucocorticoids, cyclosporin A, and prostaglandins (31).

Defects in IL-2 production or IL-2 receptor expression have been noted in a number of disease states, but in no instance has it been shown that such abnormalities are a primary feature of the disease. Among the diseases with IL-2 production abnormalities are acquired immunodeficiency (AIDS), autoimmune disease such as type 1 diabetes mellitus, systemic lupus erythematosus, and nypogammaglobulinemia (35–37). In the latter disease, the IL-2 deficiency may be responsible for the defective (lymphokine-activated killer) activity associated with the disease. However, IL-2 receptor expression defects have been seen in immunodeficiency states, multiple sclerosis, and adult T cell leukemia (38, 39).

At the moment the most important relationship of IL-2 to disease involves its use in the therapy of tumors. The basis of such therapy is that IL-2 can activate a form of natural killer cell (known as the lymphokine-activated killer cell or LAK cell) that is cytotoxic to various tumor cells (40). In preliminary studies in which high doses of IL-2 were administered with LAK cells activated in vitro, objective antitumor responses were obtained in about 20% of patients, including those with melanomas, renal cell carcinoma, and chemotherapy-resistant lymphomas (41). However, this therapy is associated with severe toxicity and requires a high degree of clinical support. Additional studies are now underway using other regimens, including those in which intermediate doses of IL-2 are administered by constant infusion or for prolonged periods with LAK cells. In addition, expansion of tumor-specific cytotoxic cells using IL-2 both in vitro and in vivo is being explored. Finally, it is possible that IL-2 administration will potentiate other antitumor therapies such as those using cytotoxic drugs and other IL.

Aside from its potential role as a antitumor agent, IL-2 may have a role as a therapeutic agent in infection, autoimmunity, and immunodeficiency. In this regard, it has been shown that IL-2 can augment specific antibody responses which are low because of specific Ir gene abnormalities and, as mentioned above. IL-2 can cause increased antigen-nonspecific cytotoxic function necessary for the destruction of potential pathogens (42).

IL-3 AND OTHER COLONY STIMULATING FACTORS (CSF)

IL-3 is representative of a family of cytokines involved in the growth and differentiation of hematopoietic and lymphoid precursor cells. This family consists of a group of molecules known as the CSF and includes the lymphokines or cytokines that share the capacity to stimulate granulocyte and/or macrophage colony formation in bone marrow cultures (43, 44). Members of this family so far identified include: 1) M-CSF (CSF-1), a heavily glycosylated 47- to 76-kDa glycoprotein that stimulates the

growth of macrophage colonies and monocytic cell lines (45). This cytokine is a disulfide-linked dimer encoded by a single gene that gives rise to related forms of the molecule as a result of alternative RNA processing (46–50). Recent evidence suggests the existence of both membrane-bound and soluble forms (49). 2) GM-CSF (CSF-α), a 14- to 35-kDa glycoprotein produced by various cells including fibroblasts, endothelial cells, and activated T cells that has growth-enhancing effects on granulocyte/macrophage/eosinophil colonies (43, 44, 51), and in combination with erythropoietin, on erythroid and multipotential colonies (52, 53). In addition, GM-CSF has effects on mature cells in that it causes neutrophil and eosinophil activation (54) and induces neutrophil phagocytosis (52). This cytokine is encoded by a gene on chromosome 5 (and is deleted in the 5q- syndrome) (55). 3) G-CSF, a 19- to 20-kDa glycoprotein produced by macrophages and/or endothelial cells that stimulates mainly granulocytes, but may have indirect effects on other precursors particularly when it is present in high concentration (56–58). As is the case of M-CSF, G-CSF is encoded by a single gene which may produce different forms of the molecule as a result of differential RNA splicing (59, 60). 4) Multi-CSF (IL-3) (also known as burst-promoting activity, mast cell growth factor, and P cell-stimulating activity), a 20- to 25-kDa glycoprotein that is derived from activated T cells and that supports the growth of virtually all types of hematopoietic progenitor cells, usually at several stages of their development (usually in concert with other CSF) (43, 44, 61, 62). This CSF is encoded by a gene on chromosome 5. 5) Erythropoietin, a 34- to 39-kDa glycoprotein produced in the kidney that predominantly stimulates erythroid precursor cells but also has effects on other precursors in association with other CSF (63, 64). It is produced by a gene on chromosome 7 (65).

The activity of multi-CSF (IL-3) on mast cell development is of special interest. In recent years, it has become clear that mast cells are separable into two types (at least in rodents), connective tissue mast cells (or typical mast cell), and mucosal mast cells (or atypical mast cell) which differ in proteoglycan, mediator, and proteolytic enzyme content (66). The development of these two mast cell types appears to be under the control of separate cytokines, the connective tissue mast cell being influenced by a fibroblast-derived factor and the mucosal mast cell being dependent on IL-3 (67). Thus, during parasitic infection accompanied by mast cell infiltration, T cells that secrete IL-3 play an essential host-defence role.

The CSF have distinct receptors distributed on undifferentiated and mature cells of various lineages (43, 44). However, since multi-CSF competes with the other CSF and GM-CSF competes with G-CSF and M-CSF, it is apparent that CSF with activity on multiple cell types bind to a number of cell lineage specific receptors (68). Of great theoretical interest is the recent demonstration that the M-CSF receptor and the oncogene product, C-fms, are identical (69). This finding links oncogene products to growth factors. To date, CSF production has been found in fibroblasts, endothelial cells, lymphocytes, and macrophages and may yet be found in other cell types as well (Fig. 2). IL-1 and TNF appear to be inducing factors for CSF production and thus monocytes, the chief source of IL-1/TNF, may play a key role in CSF production (70).

The therapeutic applications of CSF administration are currently being explored. GM-CSF administration to monkeys induces striking increases in leukocytes of most types (including erythrocytes) (71). Similar results relative to neutrophils have been obtained with G-CSF (72). On the basis of these data, GM-CSF and G-CSF may be useful in certain disease states, such as those after ablative chemotherapy for bone marrow transplantation and in infections associated with neutropenia. In addition, efforts are underway to study the effect of erythropoietin in the treatment of anemia associated with uremia (73). Finally, inasmuch as CSF may control leukemic cell growth and development, it is possible that these cytokines may play a role in the treatment of myeloid and lymphoid dyscrasias.
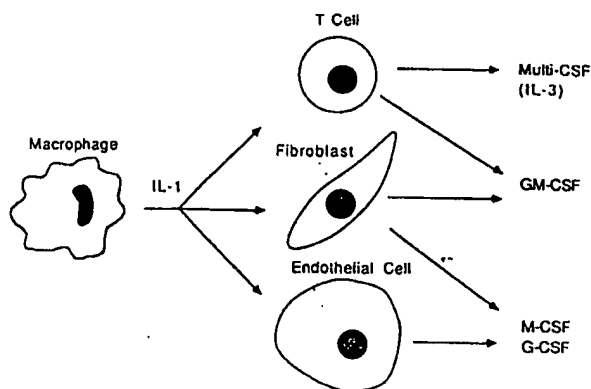

Fig. 2. CSF are produced by several cells. As shown here IL-2 can induce CSF production by these cells.

IL-4 (BCGF-I, BSF-I)

In 1982 Howard et al. (74) discovered that resting normal mouse B cells which were costimulated with anti-μ antibody could proliferate in the presence of a factor present in the supernatant of activated T cells (phorbol ester-treated-EL-4 thymoma cells) (74). This factor was distinct from IL-2 and was initially named B cell growth factor (BCGF-I or BSF-I). However, with the recognition that BCGF-I is one of several cytokines that act on B cells and that BCGF-I also acts on T cells in addition to B cells, this factor was ultimately given the designation, IL-4 (74, 75). In humans, the IL-4 gene encodes a protein of 153 amino acids, including a putative 24-amino acid signal peptide (76); thus, the deduced relative mol. wt. of the secreted protein is approximately 15 kDa, not including the additional mass due to posttranslational glycosylation. Human IL-4 has approximately 50% sequence homology with murine Il-4.

IL-4 can act on resting B cells, even before exposure to a primary stimulus: B cells preexposed to IL-4 undergo enhanced proliferation when later exposed to LPS (77). This finding corresponds to the fact that IL-4 receptors are found on the cell membrane during the G₀ phase of the cell cycle, in contrast to IL-2 receptors that are not found on the cell membrane until the cell is in the G₁ phase (78). This is not to say that IL-4 effects are limited to unactivated B cells, inasmuch as it has been shown that IL-4 also augment proliferation of activated B cells (79). Other effects of IL-4 on B cells include the induction of class II major histocompatibility complex expression (80), the expression of CD23 (low affinity IgE receptor) (81) and the up-regulation of the IL-4 receptor itself (77); these effects allow the B cell to respond to other stimulatory lymphokines and to interact with other cells.

Recently it has been shown that IL-4 plays an important role in isotype differentiation of the murine B cell: B cells stimulated with LPS in the presence of IL-4 preferentially express IgG1 (rather than IgG3) and IgE (82, 83). If this effect on isotype expression operates at the level of the isotype switching mechanism or at the level of selection of preswitched cells is not entirely clear: however, the former possibility is favored by the fact that IgG1 expression can be observed in clonal B cell populations. A related observation is that IL-4 induction of IgG1 expression is inhibited by interferon-γ (IFN-γ) and the latter itself promotes IgG2a expression (84). It is thus apparent that not only IL-4, but other lymphokines, have important effects on B cell isotype differentiation (Fig. 3). The above studies clearly establish IL-4 as a major B cell lymphokine in the mouse. It is not yet certain if human IL-4 will have similar activities on human B cells. However, data are emerging that IL-4 can selectively increase IgE synthesis by human peripheral blood B cells; on the other
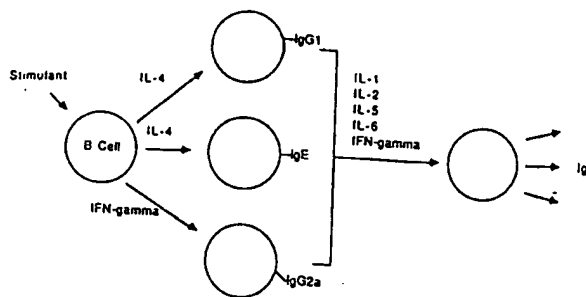
Fig. 3. IL-4 (and IFN-γ) play an important role in isotype differentiation. IL-4 leads to IgG1 production probably by directing the switch IgM B cells to IgG1 B cells. A similar mechanism may govern IL-4 enhancement of IgE B cells and IFN-γ enhancement of IgG2a B cells. As shown, a variety of factors contributes to terminal B cell differentiation.

hand, there is some evidence that IL-4 down-regulates human peripheral blood B cell responses to certain mitogens.

As alluded to above, IL-4 acts as a proliferation factor for cells other than B cells (85). Thus, IL-4 enhances T cell proliferation and causes resting T cells to undergo enhanced proliferation when exposed to other costimuli such as phorbol myristate acetate. In addition, IL-4 acts to support proliferation and expansion of immature erythroid, myelomonocytic, and megakaryocytic precursors as well as macrophages and mast cells (in the mouse). These observations suggest that IL-4 is a broadly reactive growth and differentiation factor that is not limited in its effects on any one cell type.

Recently, Mosmann et al. (86) have shown that the production of IL-4 and other lymphokines may be a property of certain T cell subclasses. In particular, these authors found that murine T cell clones can be classified into two groups: those producing IL-2 and IFN-γ, so-called TH1 cells, and those producing IL-4 and IL-5, so-called TH2 cells. The different T cell clones thus identified in vitro may represent different functional classes of T cells that arise as a result of different forms of immunologic stimulation. Thus, viral infection may induce TH1 cells and thereby evoke the production of complement-fixing IgG2a antibodies, whereas parasitic infection may induce TH2 cells and thus lead to the production of IgE antibodies and mediator release. Evidence that this is actually the case comes from studies showing that in vivo administration of anti-IL-4 monoclonal antibody inhibits IgE production in Nippostrongylus brasiliensis-infected animals (87) and conversely, in vivo anti-IgD administration, a method of inducing B cell activation and production of IL-4 by T cells, is associated with increased IgG1 and IgE production (84).

At the moment disorders of IL-4 production have not been described, although it is possible that they will be found in diseases characterized by abnormal B cell function, such as immunodeficiency states or autoimmune diseases. If indeed IL-4 proves to be a key factor necessary for IgE production, then it may be possible to modify allergic states by antagonists of IL-4 activity.

IL-5

IL-5 was initially identified as a factor present in supernatants of T cell cultures which was capable of causing B cells to either differentiate into cells actively producing antibody or to undergo proliferation; for this reason IL-5 was initially called T cell replacing factor or BCGF-II (88, 89). Further work established that IL-5 is both biochemically and functionally different from IL-4: the mol. wt. of the two lymphokines differ and IL-5 acts on cells only after initial activation, whereas IL-4 acts on resting cells (90–93). The latter fact suggests that the IL-5 receptors are

not present on resting cells as is the case for IL-4. It has not yet been determined if induction of proliferation and differentiation by IL-5 involve the same cellular mechanisms; however, these effects may sometimes be dissociated because the differentiative effects of IL-5 can occur in the absence of proliferation (94).

IL-5 has a molecular mass of 50–60 kDa and is a multimer of disulfide linked, functionally-active 18-kDa subunits (95). Cloning studies predict that the IL-5 gene encodes for a 12.8-kDa polypeptide core in humans, and that the actual 18-kDa molecular mass is due to glycosylation (96). Regarding the latter, there is one study in which it is suggested that IL-5 binds to its receptor via a lectin-like interaction involving in N-acetylgalactosamine (97).

The IL-5 receptor is as yet poorly characterized. However, as alluded to above, there is considerable evidence that its appearance on the cell surface is cell-cycle dependent and that it recognizes carbohydrate moieties on the IL-5 molecule. In addition, data have been reported that show that the gene encoding the IL-5 receptor is X-linked (98). This suggests that IL-5-controlled processes can underlie certain X-linked disorders.

Recently it has been shown that IL-5 has isotype-specific effects: after LPS activation of B cells in the presence of IL-5, IgA but not IgG subclass production is increased (99). However, such isotype specificity may be more apparent than real, because LPS alone stimulates maximal IgG subclass synthesis, so that the apparent class-specific effect of IL-5 may simply be a result of the inability of LPS alone to cause maximal IgA responses. This view is supported by the fact that in antigen-driven systems IL-5 does augment IgM and IgG responses (88). Even if IL-5 effects are not isotype-specific, it may be of particular importance to IgA B cell differentiation since IgA B cells appear to be unresponsive to certain stimuli, such as LPS.

IL-5 effects, in common with those of IL-4, are not restricted to B cells. In this regard, it has been shown that IL-5 has colony-stimulating activity for eosinophils in liquid bone marrow culture (100) and that IL-5 augments T cell cytotoxic capacity (101). The latter may relate to the fact that IL-5 induces IL-2 receptor expression.

As yet IL-5 has not been implicated in human disease. However, in view of its strong B cell proliferative and differentiative functions, IL-5 should be considered in the pathogenesis of the immunodeficiencies, particularly those marked by B cell dysfunction. This possibility obtains added weight from the aforementioned fact that genes involved in certain B cell immunodeficiencies and that encoding the IL-5 receptor may be X-linked.

IL-6 (BCDF, BSF-2, IFN-β2, HEPATOCYTE-STIMULATING FACTOR)

In recent years it has been shown that immunoglobulin secretion by the transformed B cell line CESS (102), by leukemic B cells (103), or by normal B cells stimulated with Staphylococcus aureus, Cowan I (104) could be costimulated by a soluble factor, termed B cell differentiation factor (BCDF or BSF-2) isolated from T cell lines or T cell hybridomas. The gene encoding this factor was ultimately cloned and sequenced (105) and the factor was designated IL-6; at this point, however, it became apparent that the factor was identical to IFN-β2, a substance whose gene had been cloned at essentially the same time (106).

IL-6 is a 26-kDa protein that has sequence and gene structure homology with G-CSF (106). The gene encoding this IL has several initiation sites that may be preferentially used in different tissues and that give rise to somewhat different forms of the molecule. Gene transcription of IL-6 is enhanced by IL-1, and to a lesser extent by other cytokines such as TNF, platelet-derived growth factor, and IFN-β1; in addition, LPS increases IL-6 mRNA synthesis in fibroblasts.

Unlike the other type I IFN genes (IFN-α and IFN-β1 genes) which are located on chromosome 9, the human IL-6 (IFN-β2)

gene is located on chromosome 7 (107). In addition, the IL-6 gene has only a 20% homology with other type I IFN and differs from the latter in containing large introns. These differences notwithstanding, IL-6 mediates its effects via the same receptor as other type I IFN and shares with the latter certain properties such as the ability to inhibit virus replication, to induce specific IFN-activated genes and to have antimitogenic effects on fibroblasts (108). Thus, the weight of evidence suggests that IL-6 is in fact an IFN, but one that has evolved significantly from the other IFN (108).

IL-6 has been shown to be a terminal differentiation factor that causes B cells to differentiate into plasma cells in the absence of proliferation. This is illustrated by the fact that IL-6 is essential for pokeweed mitogen (PWM)-induced Ig synthesis and that anti-IL-6 inhibits PWM-induced Ig production. Although IL-6 does not augment normal B cell proliferation, it has growth-enhancing effects on activated B cells (i.e. B cell lines). Thus, IL-6 effects on cells may depend somewhat on the preexisting state of cell activation.

In addition to its antiviral and B cell effects, IL-6 also has important up-regulatory effects on the synthesis of acute phase reactants by the hepatocyte. In this regard, IL-6 is identical to monocyte-derived hepatocyte-stimulation factor (109). The very diverse activities of IL-6 as well as the fact that IL-6 is produced by a variety of cell types indicate that IL-6 plays a central role during inflammation along with IL-1 and IFN-γ. Indeed, there is emerging evidence that many of the inflammatory activities usually ascribed to IL-1 may in reality be due to IL-6 (110–112).

TNF: TNF-α (CACHECTIN) AND TNF-β (LYMPHOTOXIN, LT)

In 1975 Carswell et al. (113) showed that the serum of BCG-primed, endotoxin-treated animals contains a macrophage-derived factor, called TNF, which was capable of causing hemorrhagic necrosis of tumors. Subsequently human TNF was purified to homogeneity (114) and based on the partial amino acid sequence of the purified material, a cDNA clone of TNF was obtained from which the full amino acid sequence was ultimately derived (115). Independently of these TNF studies, other investigators studied the mechanisms of cachexia associated with chronic inflammation (116). These studies led to the identification of a macrophage-derived factor that suppressed lipoprotein lipase synthesis (117) and that, when ultimately purified and sequenced, was found to be identical to TNF (118–120).

In yet other studies factors were isolated from activated lymphocytes which are able to lyse target cells (121, 122). Once the cDNA clone of one such factor, termed LT was identified and expressed (123, 124), it was found that the amino acid sequences of LT and TNF share 26% identity and 51% homology when conservative substitutions are made. In addition, natural and recombinant human LT share with TNF the ability to lyse tumor targets. On the basis of this structural and functional similarity, a new nomenclature was proposed: TNF-α for the macrophage factor and TNF-β for the lymphocyte factor.

Recombinant human TNF-α has a mol. wt. of approximately 17 kDa and consists of 157 amino acids whereas recombinant human TNF-β has a mol. wt. of 25 kDa and consists of 171 amino acids (125). Both TNF genes are located on human chromosome 6 near the major histocompatibility locus and in close proximity to one another; thus, it is likely that they have arisen from a common ancestral gene through tandem duplication (126).

In vivo administration of endotoxin to rabbits causes a rapid rise in TNF-α in plasma, followed by rapid clearance. The latter is thought to be caused by TNF-α membrane receptor-bearing cells present in the liver, skin, kidneys, lung, and gastrointestinal tract (127). It is now thought that many of the effects of administration of bacterial products and LPS are mediated directly by production of TNF-α (126). In addition, there is considerable evidence that TNF-α is the central mediator of the wasting that accompanies chronic disease (126). LPS is a potent inducer of TNF synthesis by macrophages, and large doses of TNF-α mimic the effects of endotoxic shock, suggesting that this protein is the major mediator of the deleterious effects of endotoxin.

TNF-α shares with IL-1 the capacity to act as a potent endogenous pyrogen; this is caused both by a direct effect on the hypothalamus and an indirect augmenting effect on IL-1 production. Other IL-1-like effects of TNF-α include the induction of prostaglandin E2 and collagenase synthesis by human synovial cells and dermal fibroblasts (128) and TNF-α-mediated bone resorption. In regard to the latter, the production of TNF-α by malignant B cells in multiple myeloma may be important to the bone lesions encountered in this disease (129). However, TNF-β has been shown to have a growth factor-like effect on human B cells and fibroblasts (130, 131).

The activities of both TNF-α and TNF-β may be due to their capacity to augment synthesis of other cytokines. In addition to the effect of TNF on IL-1 synthesis already mentioned, the TNF cause production of GM-CSF (132) and IFN-β2. In turn, other cytokines may act by causing TNF production, because it has been shown that IFN-γ and LPS can cause increased TNF production (133). Finally, the antitumor effects of TNF are enhanced by INF-γ (134).

Given their production by activated macrophages and lymphocytes, it seems likely that the TNF play an important physiologic role in the pathogenesis of human inflammatory diseases. As discussed above, they are no doubt important elements in the acute effects of endotoxin as well as in the wasting diathesis of chronic disease. Thus, antagonists of TNF may be useful in the therapy of endotoxic shock and chronic inflammatory disease. Also of possible therapeutic significance is the antineoplastic effect of TNF; however, this will only be feasible if the toxic effects of this IL can be separated from the antineoplastic effects. At this time there are no known human diseases characterized by deficiency of TNF production.

SUMMARY

As the reader of this review can readily appreciate, the IL have an almost bewildering array of functions that involve not only the lymphoid and hematopoietic systems, but also many non-marrow-derived cellular systems. The future of IL research lies in the further delineation of IL effects on cell-cell interactions and on the dissection of IL effects on intracellular processes. In addition, with the advent of recombinant IL the way is now clear to the widespread evaluation of IL or IL agonists and antagonists in a myriad of clinical studies.

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Announcements

Abstract Deadline

The American Pediatric Society and the Society for Pediatric Research announce the abstract deadline for the 1989 annual meeting (May 1–5, 1989, Washington Sheraton Hotel, Washington, D.C.) has been set as *January 3, 1989.*

For further information contact:

SPR—Ms. Debbie Wogenrich; 2650 Yale Blvd., S.E., Suite 104; Albuquerque, NM 87106; (505)764-9099.
APS—Dr. Audrey K. Brown, Department of Pediatrics, SUNY, Health Science Center at Brooklyn, 450 Clarkson Avenue, Box 49, Brooklyn, NY 11203; (718)270-1692.

International Symposium on Pediatric Rheumatology
Paris, July 21–22, 1989

The main topics of this symposium will be: New insights in the physiopathogeny of inflammatory and autoimmune disorders (cytokines, genetics...); Synovitis: Characteristics and functions of cells infiltrating the inflammatory joint; General disorders with joint manifestations in childhood; Therapeutics. General and local treatments, surgery...

Abstracts forms will be available in November 1988. This meeting is organized for the week preceding the International Congress of Pediatrics held in Paris (July 23–28).

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